

5 WHAT IS CLAIMED IS:

1. A controlled-release dosage form comprising an opioid agonist; an opioid
antagonist; and a controlled release material; said dosage form releasing during a
dosing interval an analgesic or sub-analgesic amount of the opioid agonist along
with an amount of said opioid antagonist effective to attenuate a side effect of said
opioid agonist selected from the group consisting of anti-analgesia, hyperalgesia,
hyperexcitability, physical dependence, tolerance, and a combination of any of the
foregoing, said dosage form providing analgesia for at least about 8 hours when
administered to human patients.
2. The controlled release dosage form of claim 1, wherein the dose of antagonist
released during the dosing interval enhances the analgesic potency of the opioid
agonist.
3. The controlled-release dosage form of claim 1, wherein the opioid agonist and the
opioid antagonist are released at substantially proportionate rates.
4. The controlled-release dosage form of claim 1, wherein the dosage form is
administered via a route selected from the group consisting of orally for
gastrointestinal absorption, transdermally, via oral mucosa, intranasally, via
injection, and rectally.
5. The controlled-release dosage form of claim 1, wherein the dosage form
comprises a solid, oral dosage form.
6. The controlled-release dosage form of claim 1, wherein the dosage form
comprises a transdermal delivery system.
7. The controlled-release dosage form of claim 1, wherein the dosage form
comprises an injectable formulation

- 5 8. The controlled-release dosage form of claim 1, wherein the dosage form
 comprises an intranasal formulation.
9. The controlled-release dosage form of claim 5, wherein the opioid agonist and the
10 antagonist are contained in a plurality of substrates coated with a coating
 comprising said controlled-release material, said substrates being selected from
 the group consisting of granules, pellets, beads and spheroids.
10. The controlled-release oral dosage form of claim 1, wherein the opioid antagonist
15 is treated to modify its release rate before it is combined with the opioid agonist,
 such that when the opioid agonist and the treated antagonist are combined into the
 controlled-release dosage form, the opioid agonist and antagonist are released
 from the dosage form at substantially proportionate rates.
11. The controlled-release dosage form of claim 1, wherein the dosage form is orally
20 administered and said opioid antagonist is treated to modify its release rate before
 it is combined with the opioid agonist, such that when the opioid agonist and the
 treated antagonist are combined into the controlled-release dosage form, the
 dosage form releases the agonist and the antagonist at such rate that the opioid
 agonist and the opioid antagonist are therapeutically effective over the dosing
25 interval.
12. The controlled-release dosage form of claim 1, wherein the opioid antagonist is
 present as granulates comprising the opioid antagonist dispersed in a first
 controlled release matrix, and wherein the opioid agonist is present as granulates
30 comprising the opioid agonist dispersed in a second controlled-release matrix, the
 first controlled-release matrix providing controlled-release of the opioid antagonist
 and the second matrix providing controlled-release of the opioid agonist.
13. The controlled-release oral dosage form of claim 12, wherein the oral dosage form
35 releases the opioid agonist and the antagonist at substantially proportionate rates.

5 14. The controlled-release oral dosage form of claim 5, wherein the opioid antagonist
is prepared as granulates comprising the antagonist dispersed in a controlled-
release matrix, said granulates being combined with the opioid agonist and a
further controlled release material, such that the opioid antagonist and opioid
10 against are preferably released at substantially the same proportionate rate.

15 15. The controlled-release dosage form of claim 1, wherein the opioid antagonist is
selected from the group consisting of naloxone, naltrexone, diprenorphine,
etorphine, dihydroetorphine, pharmaceutically acceptable salts thereof and
mixtures thereof.

20 16. The controlled-release dosage form of claim 1, wherein the opioid agonist is
selected from the group consisting of oxycodone, morphine, hydromorphone,
hydrocodone and pharmaceutically acceptable salts thereof.

25 17. The controlled release dosage form of claim 15, wherein said opioid agonist is a
bimodally-acting opioid agonist selected from the group consisting of morphine,
codeine, fentanyl analogs, pentazocine, methadone, buprenorphine, enkephalins,
dynorphins, endorphins and similarly acting opioid alkaloids and opioid peptides.

30 18. The controlled-release dosage form of claim 1, wherein the amount of the opioid
receptor antagonist administered is about 100 to about 1000 fold less than the
amount of the opioid agonist administered.

35 19. The controlled-release dosage form of claim 1, wherein the dosage form provides
controlled-release of the opioid agonist and opioid antagonist over about a 12 hour
period.

40 20. The controlled-release dosage form of claim 1, wherein the dosage form provides
controlled-release of the opioid agonist and opioid antagonist over about a 24 hour
period.

- 5 21. A controlled-release dosage form comprising an opioid agonist; an opioid
antagonist; and a controlled release material; said dosage form releasing during a
dosing interval an analgesic or sub-analgesic amount of the opioid agonist along
with an amount of said opioid antagonist effective to enhance the potency of said
amount of opioid agonist released from the dosage form, said dosage form
10 providing analgesia for at least about 8 hours when administered to human
patients.
- 15 22. The controlled-release dosage form of claim 21, wherein the amount of the opioid
receptor antagonist administered is about 100 to about 1000 fold less than the
amount of the opioid agonist administered.
- 20 23. The controlled release dosage form of claim 21, wherein said amount of opioid
antagonist is simultaneously effective to attenuate a side effect of said opioid
agonist selected from the group consisting of anti-analgesia, hyperalgesia,
hyperexcitability, physical dependence, tolerance, and a combination of any of the
foregoing.
- 25 24. The controlled-release dosage form of claim 21, wherein the opioid antagonist is
selected from the group consisting of naloxone, naltrexone, diprenorphine,
etorphine, dihydroetorphine, pharmaceutically acceptable salts thereof and
mixtures thereof.
- 30 25. The controlled release dosage form of claim 24, wherein said opioid agonist is a
bimodally-acting opioid agonist selected from the group consisting of morphine,
codeine, fentanyl analogs, pentazocine, methadone, buprenorphine, enkephalins,
dynorphins, endorphins and similarly acting opioid alkaloids and opioid peptides.
- 35 26. A method for enhancing the analgesic potency of an opioid analgesic contained in
a controlled release dosage form, comprising preparing a controlled release dosage
form containing an opioid agonist; an opioid antagonist; and a controlled release
material in a manner such that said dosage form delivers to human patients during
an intended dosing interval an analgesic or sub-analgesic amount of the opioid

agonist along with an amount of said opioid antagonist effective to enhance the potency of said amount of opioid agonist released from the dosage form, said dosage form providing analgesia for at least about 8 hours when administered to human patients.

27. The method of claim 26, wherein the amount of the opioid receptor antagonist administered is about 100 to about 1000 fold less than the amount of the opioid agonist administered.
28. The method of claim 27, wherein said amount of opioid antagonist is simultaneously effective to attenuate a side effect of said opioid agonist selected from the group consisting of anti-analgesia, hyperalgesia, hyperexcitability, physical dependence, tolerance, and a combination of any of the foregoing.
29. The method of claim 28, wherein the opioid antagonist is selected from the group consisting of naloxone, naltrexone, diprenorphine, etorphine, dihydroetorphine, pharmaceutically acceptable salts thereof and mixtures thereof.
30. The method of claim 29, wherein said opioid agonist is a bimodally-acting opioid agonist selected from the group consisting of morphine, codeine, fentanyl analogs, pentazocine, methadone, buprenorphine, enkephalins, dynorphins, endorphins and similarly acting opioid alkaloids and opioid peptides.
31. The method of claim 30, wherein the opioid agonist and the opioid antagonist are delivered from the dosage form at substantially the same proportionate rate.
32. The method of claim 26, further comprising: (i) pretreating either the opioid agonist or the opioid antagonist to modify its release rate; and (ii) combining the pretreated drug with the other drug to produce the dosage form in which the opioid agonist and the opioid antagonist are delivered from the dosage form at substantially the same proportionate rate.

5 33. A method for attenuating a side effect of of an opioid analgesic contained in a
controlled release dosage form, said side effect selected from the group consisting
of anti-analgesia, hyperalgesia, hyperexcitability, physical dependence, tolerance,
10 and a combination of any of the foregoing, comprising preparing a controlled
release dosage form containing an opioid agonist; an opioid antagonist; and a
controlled release material in a manner such that said dosage form delivers to
human patients during the intended dosing interval an analgesic or sub-analgesic
amount of the opioid agonist along with an amount of said opioid antagonist
15 effective to enhance the potency of said amount of opioid agonist released from
the dosage form, said dosage form providing analgesia for at least about 8 hours
when administered to human patients.

20 34. The method of claim 33, wherein the amount of the opioid receptor antagonist
administered is about 100 to about 1000 fold less than the amount of the opioid
agonist administered.

25 35. The method of claim 34, wherein the opioid antagonist is selected from the group
consisting of naloxone, naltrexone, diprenorphine, etorphine, dihydroetorphine,
pharmaceutically acceptable salts thereof and mixtures thereof.

30 36. The method of claim 35, wherein said opioid agonist is a bimodally-acting opioid
agonist selected from the group consisting of morphine, codeine, fentanyl analogs,
pentazocine, methadone, buprenorphine, enkephalins, dynorphins, endorphins and
similarly acting opioid alkaloids and opioid peptides.

35 37. A transdermal delivery system for an opioid analgesic, comprising an opioid
agonist and an opioid antagonist contained in a reservoir or matrix and capable of
delivery from the device in a controlled manner, such that when the device is
applied to the skin of a human patient, the opioid agonist is delivered at an mean
relative release rate effective to provide analgesia to said patient for at least 3
days, and the opioid antagonist is delivered at a mean relative release rate
sufficient to reduce side effects associated with the opioid agonist but not
sufficient to negate the analgesic effectiveness of the opioid.

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38. The transdermal delivery system of claim 37, wherein the amount of antagonist delivered from the transdermal delivery system is effective to enhance the analgesic potency of the opioid agonist delivered from the device.

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39. The transdermal delivery system of claim 37, wherein the amount of the opioid receptor antagonist delivered from the device is about 100 to about 1000 fold less than the amount of the opioid agonist delivered.